REMARKS

Reconsideration of the rejections set forth in the office action dated January 22, 2003 is respectfully requested. Applicants have carefully considered the points raised in the Office action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case in condition for allowance.

Applicants acknowledge Examiner's withdrawal of previous rejections under 35 U.S.C. §103(a) as being unpatentable over Wechter and Chabrier.

Rejections of Claims 1-3, 8-32, and 51-62 under 35 U.S.C. § 103(a)

A. Claims 1-3, 8-32, and 51-62 stand rejected as allegedly being obvious over Fryer, M.J., *Nutritional Neuroscience* ("Fryer"). It is the Examiner's position that Fryer makes obvious the administration of gamma-tocopherol for the treatment of both neuronal damage and ischemic conditions. The Examiner acknowledges that Fryer only teaches treatment of neuronal damage and cerebral ischemia by alpha-tocopherol, but asserts that one skilled in the art would have been motivated, in view of Fryer's teachings, to administer gamma-tocopherol, or a metabolite thereof, in place of alpha-tocopherol, to treat a symptom of neuronal damage associated with a cerebral ischemic condition. Applicants respectfully traverse this rejection, in view of the following remarks.

1. The Invention. The applicant's claimed invention is directed to a method of treating or ameliorating the symptoms of neuronal damage associated with a cerebral ischemic condition in a mammalian subject, comprising administering to the subject an effective amount or a non-alpha tocopherol enriched tocopherol composition. According to an important feature of the invention, such treatment results in a reduction of neuronal damage related to the cerebral ischemic condition in a mammalian subject, as exemplified in Example 2F (page 68) where gamma-tocopherol and gamma-tocopherol metabolite administration resulted in a decrease in total infarct

size, total ischemic damage and cerebral edema in a mammalian animal model of cerebral ischemia (rat middle cerebral artery occlusion model). Exemplary symptoms of neuronal damage associated with cerebral ischemia in a mammalian subject are further described in the specification, for example, at page 7, lines 13-19, and include, for example, reducing infarct size or tissue edema.

2. The Cited Prior Art. The Fryer reference is primarily concerned with deficiencies in vitamin E, specifically, circulating plasma levels of alpha-tocopherol, in a number of neurological pathologies. While Fryer discusses the application of alpha-tocopherol as a protective agent in certain post traumatic injuries to the nervous system (e.g. Table IV, p. 345), Fryer does not teach or disclose a method of treating or ameliorating the symptoms of neuronal damage associated with a cerebral ischemic condition in a mammalian subject by administering a non-alpha tocopherol enriched tocopherol composition along the lines of the present invention, nor does Fryer provide any motivation to do so.

3. Analysis. In order to support a claim of *prima facie* obviousness, it is incumbent upon the Examiner to show (i) that there is a motivation or suggestion in the references or in the knowledge generally available to persons of ordinary skill in the art, to modify the references or combine the teachings, (ii) that there is a reasonable expectation of success, and (iii) that the reference or references teach or suggest all the claim limitations. MPEP 2142.

Fryer neither shows nor suggests that non-alpha-tocopherols, such as gamma-tocopherol, are effective in treating or ameliorating symptoms(s) of neuronal damage associated with a cerebral ischemic condition in a mammalian subject by reducing neuronal damage. The Examiner references Table VI on page 345 of the Fryer reference as providing examples of cerebral ischemia and neuronal damage, but acknowledges that these examples only show the use of alpha-tocopherol. In Table VI, Fryer describes various other references in which alpha-tocopherol was used, alone or in combination with other therapeutics, in various models of Cerebral Ischaemia and Reperfusion Injury (CIRI). However, the Examiner does not provide

motivation to replace alpha-tocopherol by a non-alpha-tocopherol. Although the Fryer reference describes secondary references supporting the contention that gamma-tocopherol is superior to alpha-tocopherol in certain biochemical reactions, such as the detoxification of peroxynitrite, Fryer does not suggest that this biochemical activity is predictive of efficacy *in vivo*, or, more specifically, efficacy in reducing neuronal damage related to a cerebral ischemic condition in a mammalian animal.

Furthermore, neither of the two references cited by Fryer in conjunction with this biochemical activity provides motivation or suggestion to use a non-alpha-tocopherol in place of alpha-tocopherol to treat cerebral ischemia. Cooney *et al.* (1993, PNAS **90:1771-1775**; cited in IDS submitted herewith) state that gamma-tocopherol detoxification of nitrogen dioxide is superior to that of alpha-tocopherol; however, Cooney also clearly states, "γ-tocopherol possesses only 10-20% of the vitamin E activity of alpha-tocopherol in traditional bioassays, is less efficient as an antioxidant, and serum levels average 5-fold lower than alpha-tocopherol, despite the higher dietary intake of gamma-tocopherol and similar rates of absorption from the gastrointestinal tract" (Cooney *et al.*, p.1771). Applicants submit that this lesser activity of gamma-tocopherol described by Cooney actually teaches away from the concept of replacing alpha-tocopherol with gamma-tocopherol; minimally, it suggests that there would not be a reasonable expectation of success if the substitution were made.

The second reference cited by Fryer, Christen *et al.*, (1997, PNAS **94:3217-3222**; cited in Paper 11, IDS received 12/9/2002) examined *in vitro* the efficacy by which gamma-tocopherol and alpha-tocopherol inhibit peroxynitrite-induced lipid peroxidation, and found that gamma-tocopherol was more effective than alpha-tocopherol in inhibiting both peroxynitrite or SIN-1-induced oxidation of PC liposomes but not of LDL. Again, in view of these conflicting results, even if translated to an *in vivo* system, this teaching would not motivate or suggest the use of gamma-tocopherol in place of alpha-tocopherol to treat cerebral ischemia in a mammalian subject.

In view of the equivocal or conflicting results cited above with respect to the efficiency of alpha-tocopherol vs. gamma-tocopherol in other systems, applicants submit that there would be

no motivation to substitute a non-alpha-tocopherol for alpha-tocopherol to achieve the applicant's claimed invention. Further, even if one were motivated to try such a substitution, there would be no reasonable expectation of success, especially in view of the conflicting results described above.

In view of the foregoing remarks, applicants respectfully submit that the claimed invention cannot be said to be obvious over the reference cited. Applicants therefore respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a).

SUMMARY

Claims 1-62 are pending. Applicants respectfully submit that all issues raised in the Office Action have been properly addressed in this response and that the claims pending in the application are in condition for allowance. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any of the outstanding issues, she is encouraged to contact Applicant's agent at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension of time and/or other relief is required, applicants hereby petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or fees due in connection with the filing of this document to DEPOSIT ACCOUNT NO. 50-2247, referencing Docket No. 0109-UTL. Please note that this authorization does NOT authorize the Assistant Commissioner to charge the cost of any issue fee to the Deposit Account.

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